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Panel Review of Research Involving Children under Subpart D: "HIV Replication and Thymopoeisis in Adolescents with HIV"

Consultative Review—Attn: Dr. Bernard Schwetz, Dr. Irene Stith-Coleman & Dr. Leslie Ball, Office for Human Research Protections, Department of Health and Human Services

Overview of the Proposed Research:

The investigators propose a study to examine the balance between the pathogenic properties of HIV, the suppressive and selective power of antiretroviral therapy, and the regenerative capacity of the immune system that exists in HIV infected adolescents (age 13 and up, median age = 17). They argue that recent studies of the interplay between HIV infection, thymic output (thymopoiesis), and antiretroviral therapy have been critical to advances in the understanding of the pathogenesis of HIV infection and AIDS. The investigators submit that the urgency to better understand the effects of HIV on thymopoiesis is occasioned by the fact that highly active anti-retroviral therapy (HAART) has made survival into adulthood routine for infected infants and children in the US. Thus, comprehensive studies of thymopoiesis, and characteristics of HIV that impair it may guide efforts to preserve and improve immunologic functions in HIV infected adolescents. PCR methods to quantify recent thymic emigrants, and *in vivo* labeling methods to track the fate of those cells, have resulted in more comprehensive examinations of the mechanisms of T cell depletion in pediatric HIV infection. For the first time, state the investigators, methods exist to quantify the production, function and clearance of T cells.

The investigators will compare thymic function in subjects via blood collections as well as a CT scan of the thymus. A substudy will be performed during which subjects will be admitted to the Clinical Research Center overnight. Subjects will be given either an intravenous or an oral solution of deuterium, a non-radioactive marker.

The scientific aims of the investigators are:

1. To compare quantitative parameters of thymopoiesis from adolescents/young adults with perinatal HIV infection with those from age-matched seronegative control subjects, and youth with HIV infection acquired via recent adult behaviours such as unprotected sexual activity and drug abuse;

2. To evaluate the impact of viral factors on thymopoiesis of HIV-infected adolescents; and
3. To examine the T cell receptor repertoire and CTL responses of perinatally infected adolescents.

General Remarks:

A. *For children to be included in research, the IRB must find that such inclusion is scientifically and ethically appropriate, considering both general ethical principles and the specific provisions of Subpart D of 45 CFR § 46, which provide additional protections for such children.*

The first specific aim of this proposal obviates the primary questions in pediatric clinical research, "Why children?" and "Why Children Now?" The purpose of the proposed research is to understand an emerging and not well-understood HIV+ pediatric population. Most cases of pediatric Hiv-1 infection result from perinatal infection, occurring either *in utero* or during delivery. Some cases occur postnatally via transfusion or breast feeding. **Untreated pediatric HIV infection is generally followed by the development of symptomatic disease in the first year of life, and the development of AIDS in up to 50% of children by age 5**. Older children may acquire HIV infection by engaging in high risk behaviors such as unprotected sex and substance abuse. Ample studies using the methodologies proposed in the research under review have been performed in animals and adults, thus reducing the risks entailed in addressing a pediatric population.

Although a 407 panel does not engage in a consensus process relative to outcome/final report, there was complete consensus among the scientific and lay/advocate members of this panel that the scientific question is highly important and that the level of assumption of potential risk is reasonable relative to the potential knowledge gained. The clinical scientists on the panel were unanimous in their view of the study – they determined that the study, in addition to posing questions of vital scientific importance, is elegantly designed, and that the investigators are eminently qualified to conduct the proposed research. The proposed methods have already been applied to the adult population and found to be a significant addition to body of scientific knowledge. *In vivo* labeling of thymocytes with deuterium is a novel approach in the pediatric population, one that that could be highly important in terms of understanding HIV infection and resistance in children.

The lay/advocate members of the panel ardently supported the proposed research, and argued that adolescents who are HIV infected (and their

parents) would welcome this opportunity to advance knowledge regarding pediatric HIV infection and inform possible future therapy.

§46.111(a)(1) Risks to subjects are minimized; (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

The clinical scientists on the panel felt that the highest potential risk that obtains during the proposed research is for HIV-infected youth who have undergone multidrug HAART and subsequently developed glucose intolerance. This potential risk should be minimized by adding glucose intolerance as an exclusion criterion for the study, and by performing sequential serum glucose testing during the intravenous or PO administration of the Deuterated $D_{10}W$ intravenous solution or the Deuterated PO solution. The deuterium powder from which the solutions will be prepared is pharmaceutical grade, meets GMP standards (see certificates of analysis from Cambridge Isotope Laboratories, Inc. and Microtest Laboratories, Inc.), and will be prepared by the GCRC pharmacy.

Use of the CT has been reviewed and approved by the UCLA Medical Radiation Safety Committee.

§46.111(a)(3) Selection of subjects is equitable, taking into account the purposes of the research and the setting in which the research will be conducted. The research requires the use of children to answer the scientific question.

As stated above, the proposed research represents an opportunity to apply research methods that have been used in animal and adult models to an emerging and not well-understood pediatric population. The investigators may, in future, appropriately progress from an older pediatric population to a younger pediatric population.

Concern regarding the frequent or over-use of a cohort of subjects in the Los Angeles area (HIV infected adolescents) was raised during panel discussion (i.e. overstudying a clinical population due to easy availability). The clinical scientists and lay/advocate members of the panel felt that this was not problematic in this particular study, either for the HIV infected adolescents, or the normal volunteers (who form their own cohort by virtue of demonstrated high risk behaviours such as unprotected sexual behavior and substance abuse).

Concerns were raised regarding the decisional capacity of the normal volunteer population, which has demonstrated a propensity for high risk behavior, to assess the risks involved in the study. The clinical scientists and, perhaps more importantly, the lay/advocate members of the panel felt that given the minimal nature of the risks involved in the study, the use of this particular cohort of normal volunteers is appropriate, and that adequate procedural safeguards are in place to protect these children from physical, psychological, social or other harms.

Concerns were raised regarding the adequacy of the study cohort to address HIV infection and immune response in the African American population. Some genetic mutations CCR5-31 occur more frequently in the African American population. The investigators should speak to the adequacy of their proposed research to address these genetic differences among their proposed research population.

§46.111(a)(2) Risks to the subjects are reasonable in relation to the anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.

The investigators claim no benefits to individual participants either in the protocol or in assent/permission documents. This reviewer, after significant discussion during the expert panel meeting, direct questioning of the principal investigator and the IRB administrator, and review of relevant reports in the literature and by professional consultants, has determined the risks in the study to be, each individually, of minimal risk.

§46.111(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children…additional safeguards have been included in the study to protect the rights and welfare of these subjects.

Fair distribution of potential risks and benefits among potential study populations is a justice issue that inheres in any study. The potential for abuse or exploitation increases when subjects cannot make their own assessments of the relative risks and benefits of the proposed research, or when those assessment-making capabilities are not fully developed. Such potential subjects are, in effect, vulnerable to abuse by others. Thus, the standard practice, when feasible, of performing animal studies prior to human studies (although one could argue the biological or philosophical underpinnings of this approach), of studying adults prior to children, older children prior to younger children, and those with full decisional capacity prior to those with impaired or no decisional capacity.

The study population at hand, adolescent children, is, by definition, a vulnerable population.

Methods of protecting the rights and welfare of potential or actual subjects have been discussed above. They include expanding exclusion criteria to include glucose intolerance, incorporating glucose testing into the substudy, and instituting adequate provisions for protecting the privacy and confidentiality of prospective subjects or subjects relative to pregnancy testing and refusal to participate or withdrawal from the study.

Also, the investigators and their institution will provide treatment for research-related injury at no cost to the participant or his/her family (this needs to be included in assent/permission documents). As noted on pg. 17 of the protocol, subjects who are injured as a result of participating in the study will receive treatment at no cost to themselves. This reviewer highly commends the investigators and their institution for their commitment to provide such moral and tangible compensation for research injury. While not required by regulation, virtually all federal human research advisory committees have recognized compensation for research injury as a moral duty owed by the sponsors of the research. The study sponsors, the National Institutes of Health, the OHRP, and all signatories to the Common Rule should consider mechanisms for compensation for research injuries as inherent in the general ethical principles required in the federal regulation. See, for example, the Institute of Medicine report, Responsible Research: A Systems Approach to Protecting Research Participants (2002): Recommendation 6.8: "Compensate any research participant who is injured as a direct result of participating in research, without regard to fault. Because the contributions of science benefit society as a whole, it seems indisputable that society is obligated to assure that the few who are harmed in government-sponsored scientific research are appropriately compensated for study-related injuries...the same argument applies to privately funded research." P. 188. See also: Advisory Committee on Human Radiation Experiments, 1995; Department of Health, Education and Welfare, 1997; National Bioethics Advisory Commission, 2001a,b; President's Commission, 1982.

45 CFR §46.404 Research not involving greater than minimal risk
§46.102(i) Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

The proposed research is approvable under this category, given the context of the research (GCRC), the knowledge and skills of the investigators, the age of the prospective subjects, and knowledge gained from prior studies in animals and adults.

Explication:

The Report from NHRPAC: Clarifying Specific Portion of 45 CFR 46 Subpart D that Governs Children's Research (2002) addresses the interpretation of minimal risk under the Common Rule. The report is under review by DHHS, and has not been adopted as guidance by OHRP/DHHS. However, this reviewer (an author of the report) finds it useful in considering and evaluating risk in children's research. The report states:

"We interpret the definition of minimal risk to be that level of risk associated with the daily activities of a normal, healthy, average child. Risks include all harms, discomforts, indignities, embarrassments, and potential breaches of privacy and confidentiality associated with the research. Conceptually, the minimal risk standard defines a permissible level of risk in research as the socially allowable risks which parents generally permit their children to be exposed to in non-research situations. Healthy children, ranging from newborns to teens, experience differing levels of risk in their daily lives. Indexing the definition of minimal risk to the socially allowable risks to which normal, average children are exposed routinely should take into account the differing risks experienced by children of different ages…The interpretation of whether the level of risk is minimal should be one of 'equivalence of risk.' A test or procedure which entails minimal risk is one for which the probability and magnitude of harm associated with the test or procedure is equivalent to and no greater than the risk of events ordinarily encountered in the daily life of a normal, healthy, average child, or the socially allowable risks parents permit their normal, healthy, average children to be exposed to in their ordinary lives."

This reviewer finds that the proposed research does not involve greater than minimal risk, and is thus approvable under 45 CFR §46.404. She respectfully disagrees with the assessment by the UCLA IRB, which determined that "the procedures in their entirety, for the control subjects as well as the HIV+ subjects were considered more than a minor increase over minimal risk". The UCLA IRB appears to have determined, in particular, that the chest CT, the 24-hour IV infusion, the dextrose concentration (not specified in the protocol) and the deuterium-containing water constitute more than a minor increase over minimal risk (per written UCLA response to questions from the expert panel). A component analysis of individual interventions (see the National Commission on component analysis of risk, as well as Robert Levine on "the fallacy of the package deal") and contextual factors informed this

reviewer's determination that the research is approvable under 45 CFR §46.404. Contextual factors such as the location of the research interventions (UCLA GCRC), the demonstrated knowledge and skills of the research team, and the age of the prospective research subjects were paramount in this decision. Indeed, this reviewer has judged 12-hour continuous IV infusions in other pediatric studies to be greater than minimal risk.

Adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians.

In general the youth assent procedures, and the written assent document are well executed. Indeed, the introductory paragraph of the youth assent document could serve as a model to other investigators/IRBs, and the investigators should be commended on their serious and thoughtful approach to youth assent as well as to parental permission. This said, there are some improvements that need to be made in the process and the documentation.

1. Pregnancy is an exclusion criterion in the study. The investigators have not addressed the means by which privacy and confidentiality will be maintained during the initial assent process should a subject decline pregnancy screening or test positive for pregnancy, or should a subject become pregnant during the course of the study. This should be discussed both in the protocol and in the assent/permission documents. Adolescents' privacy and confidentiality should be maintain, as they may not wish to disclose pregnancy to their parents. Indeed, disclosure to parents, especially in the normal volunteer population, could be harmful to individual prospective subjects or subjects.

2. The assent/permission documents should be amended to include treatment for research-related injury at no cost to the participant as a condition of participating in the study.

§45 CFR 46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects

The proposed research is not applicable here, as the study interventions are minimal risk and provide no benefits to the subjects.

§45 CFR 46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

The proposed research is not applicable here, as the study interventions are minimal risk, the study offers no benefit to subjects, and involves healthy normal volunteers with no disorder or condition.

§45 CFR 46.407 Research not otherwise approvable but which represents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children

The proposed research is not applicable here, as the study involves minimal risk, and seeks to understand mechanisms that obtain in the relatively narrow context of pediatric HIV infection.

Final Remarks: This reviewer would like to commend the principal investigator for his sincere concern for the well being of his prospective research subjects, and for his enthusiastic and collegial interactions with the UCLA IRB and the expert review panel. She would also like to thank the administrator of the UCLA IRB and its members for their excellent work in reviewing this protocol, for their availability to the expert panel, and to their collegial interactions with the expert panel.

This reviewer would also like to commend OHRP for its dedication to the protection of human subjects of research, and for its excellent and evolving administration of the 407 review process.

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